REMARKS

I. Status of the Claims

Claims 1 and 2 are canceled.

Claims 3, 4 and 5 are amended.

Claims 3-6 are pending.

II. Claims 3-5 Satisfy 35 U.S.C § 112 First Paragraph Requirements

On page 2 of the Action, the examiner rejects claims 3-5 under 35 U.S.C § 112 first paragraph as containing subject matter not described in the specification. Also, on page 3 of the Action, the examiner states:

> A review of the present specification indicates that (ECF18R) is a candidate gene representing the *E. coli* F18 gene locus, not simply a F18 receptor.
>
> Further, an *E. coli* F18 receptor is not found in swine, it is an *E. coli* protein.

Our review of the specification, on page 2, lines 4-6 and page 8, lines 7-10, disclosed the following:

> The genetic locus for this *E. coli* F18-receptor (*ECF18R*) has been mapped to porcine chromosome 6 (SSC6), based on its close genetic linkage to the *S* locus and other loci of the halothane (HAL) linkage group on chromosome 6.
>
> In order to obtain candidate genes for the *E. coli* F18 receptor locus (*ECF18R*) 5 cosmids and one genomic clone containing the gene were isolated containing the alpha (1,2) fucosyltransferase genes, *FUT1* and *FUT2* (Meijerink *et al.*, 1997), from a porcine genomic library.

The *ECF18R*, as disclosed in the specification, refers to a porcine gene locus and not an *E. coli* gene locus (see also Exhibit A). Therefore, the amendments referring to ECF18R were adequately supported by the specification and did not represent new matter.

On page 7 of the Action, the examiner agrees that "the binding of *E. coli* in the intestine is due to the carbohydrate structure associated with the expression and activity of Fut1 [*sic*]".

The specification on page 3, lines 12-29 discloses that *FUT1* encodes for alpha (1,2) fucosyltransferase gene and is responsible for the synthesis of H antigens in the precursors of erythrocytes.

> Further information about blood groups and *E. coli* swine diseases include that carbohydrate structures of blood group antigens mediate the adhesion of some pathogenic microorganisms to host tissues, *e.g. Heliobacter pylori* adhere to Lewis^b blood group antigens, and *E. coli* causing urinary tract infections adhere to blood group *P* substance. Genes encoding glycosyltransferases that are responsible for the formation of the blood group specific carbohydrate structures, therefore, represent candidate genes for the control of bacterial colonization by the host.

Consistent with the disclosure in the specification, claims 3-5 are amended to recite "*E. coli* strains that are capable of binding to carbohydrate structures generated by FUT1. Support for this amendment can be found at least on page 3, lines 12-29 of the specification.

On pages 5-7 of the Action, the examiner contends that "the mechanism of resistance was unknown" and that "the observation of the polymorphism associated with F18 resistance represents only a correlative analysis linking a specific phenotype with a genetic polymorphism...". The pending claims relate to methods of identifying disease resistant swine and not to mechanisms of actions or resistance. The disclosed polymorphisms are useful in identifying disease resistance in swine. The markers represent a correlative analytical tool to identify swine that are resistant to *E. coli* colonization. Mechanism of action of resistance is not required by the scope of the pending claims nor by statute.

On page 7 of the Action, the examiner stated that "it would have required undue experimentation to practice the invention as claimed". Applicants respectfully disagree. The examiner provides no support for any "undue experimentation" requirement and as the Court in *Wands* stated, "routine experimentation" does not mean it is "undue".

The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in

question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998)(citing *PPG Indus., Inc. v. Gardian Indus. Corp.*, 75 F.3d 1158, 1564, 37 USPQ2d (BNA) 1618, 1623 (Fed. Cir. 1996)).

Claims 3 and 5 are amended to include "allelic association" with M307 polymorphism. Support for allelic association can be found at least on page 7, lines 17-20, and page 12, Example 8 of the specification.

The specification discloses a specific polymorphism M307 in FUT1 that is associated with resistance to *E. coli* colonization and discloses methods to identify polymorphisms by direct sequencing and correlative linkage analysis. Given M307 as an "anchor marker" in determining disease resistance to *E. coli* infection in swine and the disclosure in the specification, it is within the level of skill in the art to identify closely associated polymorphisms that are in allelic association with M307 and screen for *E. coli* infection that are capable of binding to carbohydrate structures generated by FUT1.

Applicants believe that the amended claims in light of the foregoing arguments are in allowable form and request that the 112 rejections be withdrawn.

IV. Obviousness-Type Double Patenting Rejections May Require a Terminal Disclaimer

The examiner rejected claims 3-6 over claim 1 in U.S. Pat. No. 6,596,923 (Drs. Bosworth & Vogeli; issued July 22, 2003). Although we disagree, a terminal disclaimer is being filed concurrently.

The examiner rejected claims 3-4 over U.S. Pat. No. 6,355,859B1. To the contrary, the claims are patentably distinct. The instant application claims a method of **identifying** swine that are resistant to *E. coli* by determining whether the only nitrogen base at position 307 is adenine or a polymorphism in linkage disequilibrium. The '859 patent claims a method of **improving weight gain** in swine that are susceptible to F18 *E. coli* colonization which involves first selecting swine based on the presence or absence of adenine at position 307, then second,

feeding swine susceptible to F18 *E-coli* a diet of 40% animal-based proteins which improves weight gain, while feeding other swine a diet with different percentages of animal-based protein which reduces F18 *E. coli* colonization.

These two inventions are directed towards two different problems. The instant claims do not contemplate the dietary selection of swine susceptible to *E-coli* colonization. Further, the instant claims do not deal with feeding or dietary control of pigs which are susceptible to *E-coli* colonization. It does not teach or suggest any use of feeding pigs various diets to combat F18 *E-coli* disease. Rather, the instant claims provide a method for selecting pigs which are resistant to *E-coli*. In sum, the instant claims are directed to methods of selecting pigs which are resistant to *E-coli* whereas the `859 patent is directed to a method of improving weight gain by genotype. As such, these inventions are patentably distinct and applicant requests that this rejection be removed.

VIII. Conclusion

Applicants thank the examiner for withdrawing the 102 (f) rejection. Applicants request that the pending claims be allowed. A telephone interview is requested to expedite the prosecution if there are remaining issues.

No fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 12-0913 with reference to our attorney docket number (21419-91512).

Respectfully submitted,

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1: Immunogenetics. 2000 Nov;52(1-2):129-36.

Related Articles, Lir

[SpringerLink] FULL-TEXT ARTICLE

A DNA polymorphism influencing alpha(1,2)fucosyltransferase activity of the pig FUT1 enzyme determines susceptibility of small intestinal epithelium to Escherichia coli F18 adhesion.

Meijerink E, Neuenschwander S, Fries R, Dinter A, Bertschinger HU, Stranzinger G, Vogeli P.

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The alpha(1,2)fucosyltransferases (FUT1 and FUT2) contribute to the formation of blood group antigen structures, which are present on cell membranes and in secretions. In the present study we demonstrate that both FUT1 and FUT2 are expressed in the pig small intestine. FUT1 polymorphisms influence adhesion of F18 fimbriated Escherichia coli (ECF18) to intestinal mucosa, and FUT2 is associated with expression of erythrocyte antigen 0. The FUT1 polymorphisms result in amino acid substitutions at positions 103 (Ala-->Thr) and 286 (Arg-->Glu). Tightly controlled expression of the FUT2 gene results in either an abundance or an absence of mRNA in small intestinal mucosa. ECF18-resistant animals were shown to be homozygous for threonine at amino acid 103 of the FUT1 enzyme. Susceptibility to ECF18 adhesion appeared to be solely dependent o the activity of FUT1 in intestinal epithelia. In intestinal mucosae of ECF18-resistant pigs which expressed FUT1 but not FUT2 RNA, the levels of alpha (1,2)fucosyltransferase activity were significantly lower (28- to 45-fold, $P<0.001$) than in susceptible pigs. Moreover, lysates of CHO cells transfecte with FUT1 constructs encoding threonine at amino acid position 103 also showed significantly reduced enzyme activity compared with constructs encoding alanine at this position. Our genetic and enzymatic studies support the hypothesis that the FUT1 enzyme, and particularly the amino acid at position 103, is likely important in the synthesis of a structure that enables adhesion of ECF18 bacteria to small intestinal mucosa.

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